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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/800,328	03/12/2004	Gene Michael Bright	PC25322A	1667

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PFIZER INC
150 EAST 42ND STREET
5TH FLOOR - STOP 49
NEW YORK, NY 10017-5612

EXAMINER

TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
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1624

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No. 10/800,328	Applicant(s) BRIGHT ET AL.	
	Examiner Zachary C. Tucker	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on RCE of 28 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 36-51 is/are pending in the application.
- 4a) Of the above claim(s) 48-51 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 36-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>28Dec06, 8Mar07</u> . | 6) <input type="checkbox"/> Other: _____ |

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Request for Continued Examination

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicants' submission filed on 28 December 2006, consisting of an amendment to the claims and an Information Disclosure Statement (IDS), and applicants' submission filed on 8 March 2007 of a further, supplemental amendment to the claims and of another IDS has been entered as well.

Response to Amendment

As requested in the correspondences from applicants, filed on 28 December 2006 and 8 March 2007, the claims have been amended. Also, as requested in the 28 December 2006 correspondence, the specification has been amended, to correct typographical errors and to reflect the changes made in the Examiner's Amendment included with the Notice of Allowability mailed 28 February 2006 (which was re-produced in the second Notice of Allowability pursuant to the first RCE filed in this case).

Requirement for Restriction

Requirement for Restriction between compounds (products) and methods of using the products (methods of treatment comprising administering the products to a subject) is proper, as explained in the MPEP, chapter 806.05(h). Applicants are advised that methods of use that are commensurate in scope with the elected products (should products be elected in response to this Requirement) will be rejoined at such time that claims drawn to the elected products are in condition for allowance. In the instant case, this restriction practice necessitates that the compounds according to claims 36-46, and new claim 47,

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drawn to a pharmaceutical composition, be considered as the invention to be examined (because those claims are drawn to 'products'), constructively elected by original presentation, in accordance with 37 C.F.R. 1.145, as explained in MPEP 818.02(a). Filing of a Request for Continued Examination does not re-start the examination process, it continues examination – an election in the case prior to the filing of an RCE still stands after RCE filing.

The claims are to be Restricted as follows:

Group I – Claims 36-47, drawn to compounds described by the molecular structure diagrams shown in claims 36 and 38, those compounds named in claim 40 (claim 40 is an independent claim), and a pharmaceutical composition comprised thereof, according to newly submitted claim 47

Group II - Newly submitted claims 48-51, directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product. See MPEP § 806.05(h). In the instant case, many of the disorders recited in the newly presented method-of-treatment claims are treatable with a wide variety of materially different agents, such as administering prior art dopamine D2 receptor antagonists (e.g., chlorpromazine, haloperidol, risperidone) for the treatment of schizophrenic type disorders.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 48-51 are withdrawn from consideration as

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being directed to a non-elected invention, although they will be rejoined at such time that the elected invention is in condition for allowance. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

When the Office makes a determination of whether or not a claimed invention is enabled by the accompanying disclosure, an analysis of the factors promulgated by the court in the *In re Wands* decision are customarily relied upon. These so-called “Wands factors” are as follows, and each in turn will be addressed for the claimed solvates:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) Insofar as the solvate embodiment of claims 36-47 is concerned, those claims read on solvates of the claimed compounds, with *any* solvent. The definition of a solvate, taken from the Vippagunta et al reference, cited in section (C), (D), (E) below, is a “crystalline solid adduct[s] containing solvent molecules within the crystal structure, in either stoichiometric or nonstoichiometric proportions, giving rise to unique differences in the physical and pharmaceutical properties of the drug.” In other words, the claims read on a huge number

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of special solid forms of the compounds, because there are so many different *solvents* known to those of ordinary skill in the chemical arts.

(B) The nature of the invention is that of a chemical compound, a pharmaceutical composition or a medical treatment method, wherein the compound is in a special physical form.

(C), (D), (E) Solvates, at the time the invention was made, were known to exist and can be identified, and many had indeed been documented in the literature, but the level of skill in the art had not progressed to such an extent that the directed preparation of those solvates other than hydrates was routine or simple. The following references address the state of the art with respect to crystalline forms of organic compounds, formation of solvates of organic compounds, and the lack of predictability thereof.

Vippagunta et al, "Crystalline Solids" Advanced Drug Delivery Reviews, vol. 48, pages 3-26 (2001).

and

Gavezzotti, "Are Crystal Structures Predictable?" Accounts of Chemical Research, vol. 27, pages 309-314 (1994).

First, it is evident from both of the references that formation of specific crystalline forms, and more particularly, solvates, is highly unpredictable. See Gavezzotti, page 312, point #8, and Vippagunta et al, page 11, "Prediction of Polymorphs" and page 18 "Prediction of the formation of hydrates and solvates."

Because the formation of solvates is unpredictable, even the relatively high level of skill possessed by one of ordinary skill in the art is not enough to render preparation of solvates routine. Each solvate of each compound must be experimentally prepared (since the conditions necessary for the formation cannot be predicted), and all of the factors relevant to each individual compound's ability to crystallize must be studied. These factors are identified in points #1-7 of the Gavezzotti reference. The preparation of each single

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claimed solvate represents a significant undertaking in the areas of preparative organic chemistry, physical chemistry, and crystallographic measurements. In order to create the solvates of compounds according to the present invention, one of ordinary skill would engage in a laborious trial-and-error process for each one of the solvates of each one of the compounds embraced by present claims, with every solvent.

It is unknown that the full scope of solvates of compounds of formula (I) is even possible (see Gavezzotti, page 309, point #1).

(F) Aside from a mention that the invention includes solvates, no guidance relevant to preparation of solvates is provided in the disclosure.

(G) No working examples demonstrate the preparation of a solvate. In fact, the description of synthetic schema by which the compounds of the invention are made, appearing on pages 16-24 of the specification (particularly page 24) teaches that compounds of the invention are isolated from a variety of solvents, such as methanol or ethanol, yet not solvate of any compound with any of the solvents employed is identified. This is further evident from the examples section of the specification, where no solvate of a compound of the invention is identified, despite having been crystallized from solvents.

(H) Each compound embraced by the instant claims, of which there are many thousands, as a solvate with every solvent within the scope of the term "solvate" generally, of which there are also many thousands, would require the efforts of many researchers over a period of years. Those efforts are potentially inconclusive. For one of ordinary skill in the art to conduct the type of research outlined in Gavezzotti and in Vippagunta et al for preparation of every one of the claimed solvates would be undue. "A solvate" of a chemical compound is much more complex than simply a mixture of a compound with some solvent. A grant to applicants of a right to exclude others from making all solvates of

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compounds embraced by the instant claims is unwarranted in light of the complete lack of any direction as to how one of ordinary skill would do so.

**Comments
~and~
Allowable Subject Matter**

Deletion of reference to "solvates of" the compounds in the claims, in all occurrences, would overcome the rejection under 35 U.S.C. 112, first paragraph which is set forth in this Office action. Claims 36-47 would then be allowable, for the same reasons given in the Notice of Allowability mailed 28 February 2006.

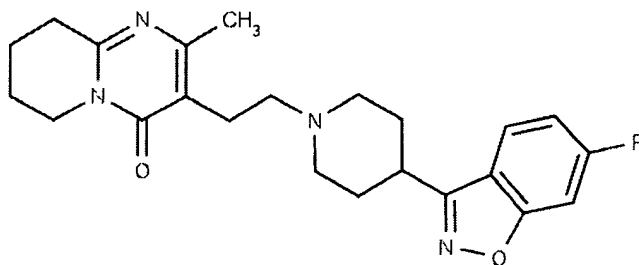
In addition to the close prior art cited and summarized in the Notice of Allowability mailed 28 February 2006, the examiner would cite the publication WO 00/39128, which was identified as an "X" reference in the International Search Report for the international application corresponding to this U.S. application. That publication discloses compounds like those according to the instant claims, except that the atom at the position corresponding to "X" in instant claims 36 and 38 is -NH-, where it is oxygen in the instant claims. Also, WO 00/39128 teaches a generic formula wherein the ring corresponding to the pyridin-2-yl group in instant claims 36 and 38 is either pyrimidinyl or pyridyl. The group corresponding to "X" in the instant claims, in WO 00/39128 is required to always be -NH-; it cannot be oxygen according to the teachings of that publication.

Should reference to solvates be deleted, in all occurrences, in order to obviate the outstanding enablement rejection, claims 48-51, drawn to methods of treating various disorders, will be rejoined and the Requirement for Restriction will be withdrawn. The full scope of the methods of claims 48-51 is not enabled (nor are the solvates referred to in those claims - the "solvates" limitation in claims 48-51 must be deleted as well, additionally to preserve antecedent basis in the independent claims). Claims 48 and 50 in

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fact would include any and all disorders of the Central Nervous System (CNS), a huge number of distinct medical conditions, many of which have nothing to do with dopamine or serotonin receptors of any kind. Conditions that are not connected with function of dopamine and serotonin receptors cannot possibly be affected by, much less treated by, a compound according to the present invention, whose activity is antagonism of 5-HT_{1B}, 5-HT_{2A} and D₂ receptors. Though claims 49 and 51 name a series of specific conditions, instead of "central nervous system disorders," generally, those two claims are not enabled, because a drug which acts as an antagonist at 5-HT_{1B}, 5-HT_{2A} and D₂ receptors was not, at the time the invention was made, understood by a physician of ordinary skill to be a plausible (or effective, for that matter) treatment for each of these recited conditions.

A review of the medical literature, to determine the therapeutic utility of drugs which have antagonism at 5-HT and dopamine receptors, specifically 5-HT₂ receptor subtypes and dopamine D₂ receptors, was conducted as a preliminary measure in preparation of this Office action. The drug risperidone, marketed as Risperdal®, has antagonist activity at 5-HT₂ and D₂ receptors, and has been used as a therapeutic agent for some time. It is an antipsychotic drug, and has good efficacy in treatment of schizophreniform conditions, dementia and delirium. Risperidone has a molecular structure similar to the compounds according to the present claims as well as having a similar pharmacological activity:



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According to these two references:

Janssen et al, "Pharmacology of Risperidone (R 64 766), a New Antipsychotic with Serotonin-S₂ and Dopamine-D₂ Antagonist Properties" *The Journal of Pharmacology and Experimental Therapeutics* vol. 244(2), pages 685-693 (1988).

and

Keks and Culhane "Risperidone (Risperdal): clinical experience with a new antipsychotic drug" *Expert Opinion on Investigational Drugs*, vol. 8(4), pages 443-452 (1999).,

risperidone, at the time the invention was made, was understood by those of ordinary skill in the art of treating central nervous system disorders to have utility for treating schizophrenia and related delusional-type disorders. It is classified as a *neuroleptic* drug, as would be the compounds of the present invention, Neuroleptics (such as risperidone) cannot treat cancer, Alzheimer's disease, chemical dependencies, and depression (all recited in claims 49 and 51), and would actually make movement disorders like Parkinsons disease worse, because they are dopamine antagonists. Parkinsons disease is a condition resulting from too little dopamine in the CNS. A neuroleptic drug cannot increase intellect, therefore, a compound of the present invention would not be a treatment for "a deficiency in memory, intellect, or learning and logic ability" or mental retardation. Agents employed for treatment of restless legs syndrome are dopamine agonists, such as pergolide, or opioid receptor agonists, such as oxycodone or the new agent ropinorole, which has activity primarily at dopamine receptors, but possess moderate activity at opioid receptors.

The Keks and Culhane reference, incidentally, teaches that antipsychotic drugs may actually exacerbate depression (page 444, 3rd and 4th line up from the bottom of the page).

Another reference, discovered in the search conducted in order to determine what the state of the art in therapeutic utility of drugs which have antagonist activity at 5-HT_{1B}, 5-HT_{2A} and D₂ receptors, was the following article:

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Hirota et al, "Neuropharmacological Profile of an Atypical Antipsychotic, NRA0562" *CNS Drug Reviews*, vol. 9(4), pages 375-388 (2003).

which reports a new compound, dubbed "NRA0562," that has antagonist activity at 5-HT_{2A} and D₂ receptors. The drug is taught to be a treatment for psychoses and schizophrenia-type disorders.

At the time the invention was made, the physician of ordinary skill only recognized treatment of psychoses and schizophrenia-type disorders with drugs having the same activities as do the compounds according to the invention.

Cancellation of claims 48 and 50, and amendment of claims 49 and 51 so as to limit those claims to a method of treating a disorder (by administering a compound of claim 40 or claim 36, or the (*R*) or (*S*) enantiomer thereof, or the *cis*- or *trans*- isomer thereof, or a pharmaceutically acceptable salt thereof) selected from the group consisting of schizophrenia, a schizophreniform disorder, a schizoaffective disorder, a delusional disorder, a substance-induced psychotic disorder, a personality disorder of the schizoid type, dementias, a schizoaffective disorder of the delusional type or the depressive type, psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants or phencyclidine (opioids do not cause psychosis, and therefore "opioids" should be struck from this part of the Markush group), multi-infarct dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia, Alzheimer's-related dementia, delirium and Tourette's syndrome would be allowable if all other issues in this Office action are addressed. Claims 49 and 51 would be rejoined and allowed upon receipt of an amendment corresponding to the suggested changes in this paragraph.

Information Disclosure Statements

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Two Information Disclosure Statements (IDS's) have been submitted pursuant to the present RCE filing of 28 December 2006. Both have been considered, and signed and initialed PTO forms 1449 to that effect are included with this Office action. On the PTO 1449 form accompanying the IDS filed 8 March 2007, the patent cited thereon has been "lined through" because it is a duplicate citation. That patent was cited in the IDS filed 15 November 2004 and a signed and initialed form PTO 1449 to that effect was mailed to applicants with the Notice of Allowability on 28 February 2006.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Monday to Friday from 5:45am to 2:15pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.


ZACHARY C. TUCKER
PRIMARY EXAMINER